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Applicant: HANGZHOU MINSHENG PHARMACEUTICAL CO.,LTD etc.

Transmittal Letter for the Amendment of Specification

Honorable Examiner of the State Intellectual Property Office of the People's Republic of China:

After careful review, we have found some clerical errors in the previously submitted specification of the application. Now, we want to make an amendment as follows, upon your approval:

On page 10 of the specification, in the part of "Explanations for Figures":

In row 8 (from bottom): "Fig.1: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, where isopropyl ether was used as solvents;" should be replaced with "Fig.1: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, wherethe mixture of isopropyl ether and heptane were used as solvents;"

In row 5 (from bottom): "Fig.3: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, where ethanol was used as solvent;" should be replaced with "Fig.3: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, where ethanol solution was used as solvent;"

Enclosed with the letter is the page needed for replacement.

Sincerely,

Applicant: HANGZHOU MINSHENG PHARMACEUTICAL CO.,LTD etc.

Agent: HANGZHOU JINTONG PATENT AGENCY CO.,LTD

Patent Agent: HU Hongjuan

TEL/FAX: 0571-56837278

E-mail:chhu@hzcnc.com

ether and hexane or heptane; the most preferred are 70% ethanol solution , the mixture of isopropyl ether and hexane (v/v=1:2) , the mixture of isopropyl ether and heptane (V/V=1:2). The other proper solvents can easily be decided by ordinary technicians of the present domain. The crystallization can be carried out either by evaporating the solvent or by cooling down the solution. The crystallization temperature is different according to the solvent and the crystallization mode, which can easily be decided by ordinary technicians of the present domain. The crystallization temperature can be any proper temperature between -40 ℃ and the boiling point of the solvent, the preferred temperature is between -20 ℃and 60℃, the more preferred temperature is between -5℃ and room temperature. Citalopram diol intermediate can also be crystallized directly from the oil substance without adding any solvent. The conditions of crystallization can easily be decided by ordinary technicians of the present domain.

Citalopram diol intermediate free alkali can be resoluted through crystallization. Through the crystallization of the racemic citalopram diol intermediate free alkali crystal, a mixture of S- and R- citalopram diol intermediate with more than 50% of one of the enantiomers is resoluted. The resolution can be carried out by dissolving the racemic citalopram diol intermediate in proper solvent. The solvent used is the same as that described previously, it can be methanol, ethanol, acetone, acetonitrile, ethyl ether, toluene etc. and the mixture of them: methanol and water, ethanol and water, acetone and water, acetonitrile and water etc. The resolution can also be carried out directly in the oil substance without adding any solvent.

Through ordinary purification, the purity of citalopram free alkali or S-citalopram free alkali and their acid addition salts obtained after ring closure through the present invention is over 99.5%(w/w), the preferred purity is 99.8%(w/w), and the purity of S-citalopram free alkali and its acid addition salts is over 97%(w/w), the preferred purity is 99%(w/w). Wherein, ordinary purification refers to: the product is disposed with active carbon and/or silica gel; the free alkali is purified through salt formation with acid, and/or the salt is extracted and set free with alkali, and/or the salt is purified through crystallization.

The racemate used for resolution can either be the obtained purified or unpurified citalopram diol intermediate oil substance or its hydrobromic salt, sulfuric salt, hydrochloric salt and oxalate salt etc., preferably the quite pure citalopram diol intermediate free alkali prepared through the present invention.

Explanations for Figures

Fig.1: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, where the mixture of isopropyl ether and heptane were used as solvents;

Fig.2: The XRD spectra of the prepared citalopram diol intermediate alkali crystal of Fig.1.

Fig.3: The DSC profile of citalopram diol intermediate alkali crystal prepared as described in Example1, where ethanol solution was used as solvent;

Fig.4: The XRD spectra of the prepared citalopram diol intermediate alkali crystal of Fig.3.

EXAMPLES

Example 1 Preparation of high pure citalopram diol intermediate alkali crystal racemate